UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,098	06/20/2006	Steffen Goletz	10913.0003-00000	8158

22852 7590 10/07/2009

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
LEAVITT, MARIA GOMEZ	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
10/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ATTACHMENT TO ADVISORY ACTION

Continuation of 3. NOTE: Amended claim 1 introduces specific limitations, i.e., "a cell line which synthetizes and expresses on the cell surface" . None of the claims previously examined recited " a cell line which synthetizes and expresses on the cell surface " . This limitation was not previously examined requiring new search and consideration of the art made of record, and of the specification for support of the amendment. Therefore, the amendment to the claims filed on 09-23-2009 has not been entered.

Continuation of 11. does NOT place the application in condition for allowance because: Applicants' arguments rely upon and are directed to the proposed amendments, e.g., pages 11 and 15. As the claims' amendment has not been entered, applicants' arguments based on the proposed amendment are not persuasive. Additionally, non patent literature publication by Brossart et al., Cancer Research 61:6846-50 (2001) constitute evidence that is newly presented. As the non patent literature publication has not been entered and applicants' arguments are based on the non patent literature publication are not found persuasive (see page 8 of Applicants' remarks filed on 09-23-2009).

Response to Applicants' arguments no directed to the proposed amendments

Withdrawn Objections/Rejections in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 112- First paragraph- written description

In view of Applicants' arguments and the disclosure in the specification as filed at page 8, lines 11-17, defining the term "subclones" as

> "said term relates preferably to the specific cell-clones NM-F9 and/or NM-D4 as well as subclones thereof. The meaning of "subclones" is described herein elsewhere. The term "NM-F9" as used herein, is equivalent to terms like e.g. "F9"; "clone F9" or "K562-F9" and relates to cells of a cell line or a cell line deposited with the Deutsche Sammlung fur Mikroorganismen und Zellkulturen GmbH ("DSMZ") on Aug. 14, 2003 and having the deposit number DSM ACC2606" ,

rejection of **claim 3 subpart (c)** under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn as applicants are in possession of the F9 and D4 cell lines and subclones therefrom.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Rejections/objections maintained in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 112-Enablement

Claims 20 and 22 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The specification does not provide enablement for claims directed to methods of treating or preventing lymphoma in a subject by administering a cell line expressing TF, MUC1 and glycophorin on its surface as broadly claimed. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim.

Response to Applicants' Arguments as they apply to rejection of Claims 20 and 22 under 35 U.S.C. 112, first paragraph

At pages 6 and 7 of the remarks filed on 09-23-2009, Applicants essentially argue that: 1) the only technical support for the allegation of unpredictability in treating cancer I Carbone, however, Carbon does not support a general allegation that treating cancer is

unpredictable, but is simple a review article discussing the identification and classification of carcinogens, 2) Carbone merely reiterates the potential problem of treating cancers by a single-target approach because of genetic heterogeneity in cancer, 3) the claimed methods avoid the problem stated by Carbone because it uses cells that express several pan-carcinomic markers; TF and MUC1 have been recognized as useful antigens in immunotherapy, see Goletz et al., (*Advances Expt. Med. Bio.* 535, 147-62, 2003) for a description of using TF in a variety of immunotherapies, 4) Czuczman et al., (*J. Clin. Oncol.* 1999, pp.268-76) uses CD20 antibodies to treat lymphomas, and 5) the art provides sufficient guidance for use of treating cancer by immunotherapy, including using TF, MUC1 and glycophorin as protective antigens, and knowledge that MUC1 is expressed in a variety of lymphomas and for the skill artisan to make and use the claimed methods for treatment/prevention of cancers as encompassed by claims 20 and 22 without undue experimentation. Such is not persuasive

Regarding 1) and 2), Carbone et al., corroborates the unpredictability of a treating or preventing solid tumors which are genetically heterogeneous both among cases and within the same patient. There is not sufficient evidence that the claimed invention "avoids this problem" as applicants assert. Though Applicants ccontemplate that NM-F9, for example, could be administered directly to a subject and, because of the hypersensitivity of NM-F9 to NK cells, NM-F9 would be lysed by NK cells leading to exposure of dendritic cells (DC) to necrotic lysates of transformed NM-F9 resulting in maturation of DC and induction of naive cytotoxic T cells against MUC1 and AGPA expressed in functional mature dendritic cells as well as expressed in lymphoma cells, there is not evidence of how the contemplated activation of naive cytotoxic T cells

against MUC1 and AGPA would constitute and effective immune response against lymphoma so as to treat or prevent this form of human cancer.

Regarding 3), Goletz et al., merely contemplates a therapy of mediating interaction of TF with ASGPR of the hepatocytes to prevent liver metastasis (Goletz et al., 2003, Advances in experimental medicine and biology, pp. 147-62; p. 156, last paragraph). Moreover, the author highlights conflicting results in early developmental tumor vaccines and further contemplates TF as a tumor marker for passive and active immunotherapy (p. 159). The specification as filed fails to provide particular guidance to resolve the known unpredictability in the art associated with treatment of lymphoma in a subject which included *de novo* determination of effective target sites, modes of delivery, safe administration of at least transformed NM-F9 cells to by lysed by NK cells so as to lead to maturation of DC and induction of naive cytotoxic T cells against MUC1 and AGPA to appropriately target lymphoma cells, requirement for repetitive treatment, level of expression required, cell number and others, and further, whereby treatment effects are provided for the claimed lymphoma condition.

Regarding 4), Czuczman et al., provides further insight into the unpredictability of treating different types of lymphomas (Applicants' elected species) when he disclose that patients with low-grade or follicular B-cell non–Hodgkin's lymphoma received a chimeric anti-CD20 antibody, Rituxan, in combination with standard-dose systemic chemotherapy (Czuczman et al., *Journal of Clinical Oncology*, 1999: 268-276, Abstract) whereas patients with lymphoma of the mucosa-associated lymphoid tissue (MALT) are treated with chemotherapy by using the nucleoside analog cladribine (Jaget et al. *Journal of Clinical Oncology*, pp. 3872-3877) clearly indicating different treatments depending on

the type of lymphoma . Hence, there is not evidence in the disclosure of how to practice the invention as it is claimed in its current scope without undue experimentation.

Regarding 5) the fact that the present working examples demonstrate *in vivo* induction of IgG and IgM antibody responses in NOD/SCID mice reconstituted with human PBMC that were vaccinated with NM-F9 cell lysates is not disputed. However, beyond this effect there is no evidence that delivery of NM-F9, NM-D4 alone or combinations thereof, would treat or prevent any type of mucosa-associated lymphoid tissue, B-cell lymphoma, T cell lymphoma, gastric lymphoma in a subject, including a human subject as broadly claimed.

Claim Rejections - 35 USC § 102

Claim 1 remains rejected under 35 U.S.C. §102(b) as being anticipated by Ichiyama M (2000, Kari Igaku Kenkyusho Zasshi, JP vol. 51, no. 3-4, pages 93-110, of record) as evidenced by Benoist et al., (1992, Immunology Letters, pp. 45-55) and Karsten et al., (1998, Cancer Research pp. 2541-2549, of record)

Response to Applicants' Arguments as they apply to rejection of Claim 1 under 35 USC § 102

At pages 9-10, Applicants essentially argue that: 1) the Examiner appears to believe that TF is necessarily present in the MUC-1-transformed K562-dereived cells of Ichiyama though it cannot be detected due to the presence of terminal sialic acids preventing its detection, 2) the Examiner appears to believe that any carbohydrate structure that contains a core-1 unit "expresses TF"; however, TF corresponds to exposed core-1 (Gal1-3GalNAc) see specification at page 6, line 10, 3) TF corresponds to core-1

without additional carbohydrates, such as terminal sialic acids and more complex carbohydrate structures that contains core-1, and 4) Applicants allege that TF can only be detected in K562 cells after enzymatic cleavage of the sialic acid structures with neuraminidases which underscores that these cells do not express TF. Such is not persuasive.

Regarding 1), 2), 3) and 4), the specification at page 6, line 18, cites that "as prerequisites for an expression of the inner core sugar Core-1, which equals TF when exposed were very difficult". Claim 1 as written does not place any limitation on whether the TF is exposed or hidden as part of larger sugar core-1 molecule, naked, further glycosylated, elongated with any degree of sialylation. Accordingly, the claims are broadly but reasonably interpreted as expressing core-1-containing structures that also contain additional sialic acid structures. Moreover, the fact that enzymatic desialylation with neuramidase treatment leads stable expression of the core glycotope TF, appears to suggest that TF was present in K562, however, access to the TF glycotope in MUC1 and/or glycophorin was blocked by the presence of terminal sialic acids in the MUC1 and/or glycophorin. How could expression of TF in NM-F9 and NM-D4 be explained if the glycotope was absent in parental K562?.

Claim Rejections - 35 USC § 103

Claims 1, 5, 6, 11, 12 and 24 remain rejected under 35 USC 103 as being unpatentable over Ichiyama M (2000, Kari Igaku Kenkyusho Zasshi, JP vol. 51, no. 3-4, pages 93-110, of record) as evidenced by Hinoda (2005, Journal of Clinical Laboratory Analysis, pages 100 – 104, Abstract), in view of Benoist et al., (Immunology Letters 1992, pp. 45-55) and Karsten et al., (1998, Cancer Research pp. 2541-2549, of record)

and further in view of Horton et al., (U.S. Patent 7,268,120, Date of filing Apr. 21 2000).

Response to Applicants' Arguments as they apply to rejection of Claims 1, 5, 6, 11, 12 and 24 under 35 USC 103

At pages 10-11, Applicants essentially argue that: 1) the Examiner has dismissed Applicants' report of unexpected an beneficial results e.g., IgG response elicited by lysates of the cells of the invention as an inherent property of the cells, 2) the only disclosure of TF antigen in the combined references is by Karsten who reports MUC-1-derived peptides engineered to contain TF and Horton's erroneous suggestion that TF is an immunogenic polypeptide, and 3) the core-1 motif in K562 cells is obscured by terminal sialic acids and is therefore unable to elicit an immune response as evidenced in the instant invention with the ability of cell lysates to elicit an immune response. Such is not persuasive.

Regarding 1) and 3) the Examiner has previously acknowledged in the office action of 01-27-2009, at pages 8-9, that Fig. 6 illustrates that naive CTL can be activated against these MUC1 and AGPA antigens by using NM-F9 lysates (page 55, lines 19-23). Moreover, the specification discloses *in vivo* induction of an IgG and IgM antibody responses in NOD/SCID mice reconstituted with human PBMC that were vaccinated with NM-F9 cell lysates, indicating induction of T helper immune responses and memory immune responses against MUC1, TF and AGPA (p. 55, lines 24-30). Furthermore, the specification teaches that NM-F9 and NM-D4 cells are more sensitive to the cytolytic activity of NK cells than K562 wt because of a very low degree of sialylation on the cell surface (p. 56, lines 25-26), which is in contrast to the literature wherein sialylated

carbohydrates have been described to mediate the cytotoxic lysis by NK cells (p. 58, lines 18-24). However, the specification is silent about *in vivo* administration of any cell line which expresses on the cell surface TF, MUC1 and glycophorin other than NM-F9 and NM-D4 other than F9 and D4 cell lines and subclones therefrom. Note that the recitation of the TF in claim 1 is broadly but reasonably interpreted as exposed or hidden as part of larger sugar core-1 molecule, naked, further glycosylated, elongated with any degree of sialylation. The combined disclosure of Ichiyama, Hinoda, Benoist, Karsten and Horton would obviate the instant cell line as claimed, accordingly, any characteristics or properties of transformed cell line K562 with human mucin MUC1cDNA such as processing of the core-1 motif in the MUC1 DTR repeats as by NK lysis would be anticipated by the recitation of an intended use as no structural limitations is added by the intended use.

Regarding 2), Ichiyama M, discloses the cell line K562 contransfected with tumor-associated epithelial human mucin MUC1cDNA. Karsten discloses the presence of the TF antigen (Galβ1-3GalNAcα-O-Ser/Thr (Core 1)) and Tn antigen (GalNAcα-O-Ser/Thr) at different single and multiple positions within the immunodominat region of the MUC1 repeat. Thus, Karsten complements the teachings of Ichiyama M by disclosing that K562 cells transformed with the MUC1cDNA encoding for the full length tumor-associated epithelial human MUC1 implicitly comprising TF in the tandem repeat of the DTR motif (see for example, page 2545, col. 2; p. 2549, col. 1). As the TF is located on the MUC1 DTR repeats and MUC1 is located on the surface of K562, it follows that TF is on the surface of K562. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where

the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Claim Rejections - 35 USC § 103

Claims 1 and 23 remain rejected under 35 USC 103 as being unpatentable over Ichiyama M (2000, Kari Igaku Kenkyusho Zasshi, JP vol. 51, no. 3-4, pages 93-110, of record) in view of Benoist et al., (Immunology Letters 1992, pp. 45-55) and Karsten et al., (1998, Cancer Research pp. 2541-2549, of record) and further in view of Springer G (1997, J Mol Med, pp. 594-602, of record.)

Response to Applicants' Arguments as they apply to rejection of Claims 1 and 23 under 35 USC 103

At page 15, of remarks, Applicants' essentially allege that a cell enzymatically treated to remove sialic acid moieties does not express TF or asialoglycophorin, since, as is known in the art, expression relies on the cell's own synthesis machinery. As the claims' amendment has not been entered, applicants' arguments based on the proposed amendment are not persuasive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

Maria Leavitt
Primary Examiner, Art Unit 1633